Status of Claims

Claims 116 to 185 are pending in the application. Claims 116 and 164 are amended herein. Claim 185 has been added. No claims have been canceled. Claims 132 to 137, 142 to 145, 152 to 159, 161 to 163, 167 and 175 to 177 have been withdrawn from consideration by the Examiner, as being directed to non-elected species.

The Amendments

The amendments to Claims 116 and 164 are made to clarify the steps and intended result of the methods of the present invention. As amended herein, the claims define methods for enhancing the delivery of a bioactive agent to a selected tissue in a patient. The methods utilize application of ultrasound energy to induce cavitation or rupture of a vesicle composition, or activation of an acoustically active composition. Claim 116 specifies that ultrasonic energy is applied in *an amount sufficient* to increase delivery of the bioactive agent *from* the vasculature *into* the selected tissue. Claim 164 and newly added Claim 185 (which depends from Claim 116) specify that the ultrasound energy *has a frequency of from about 100 kHz to about 1MHz*. The amendments are supported in the specification, for example, by Examples 13 to 15, which describe the administration of ultrasound in the claimed methods, at frequencies of 200 kHz, 1 MHz, and 100 kHz, respectively, to enhance the delivery of the bioactive agent to the target tissue.

Response to Rejections

Rejections over Siegel

In the Office Action dated December 26, 2001, Claims 116 to 131, 138 to 141, 146 to 151, 160, 164 to 166, 168 to 174 and 178 to 184 stand rejected under 35 U.S.C. §§ 102(b) and/or 103, over Siegel et al, U.S. Patent 5,695,460 ("Siegel"). Applicant respectfully disagrees with the Examiner that these claims, in their previous form, were anticipated or rendered obvious by Siegel. Applicant further respectfully submits that the amended claims clearly define over that reference.

Siegel is directed to methods for dissolving arterial thrombi (*i.e.* thrombi *within* the blood vessel). *See* col. 2, lines 2 to 5. The methods described by Siegel comprise injecting a patient with an echo contrast agent, either alone or in conjunction with a thrombolytic agent such as streptokinase, followed by the application of ultrasound. *See* col. 5, lines 17 to 28. As a result of the combined use of the echo contrast agent and ultrasound application, Siegel states that one may produce "substantial dissolution of the thrombosis without the need for the introduction of thrombolytic agents" (*see* col. 5, lines 26 to 28), or one may "effect removal of the thrombosis in less time than required by the activity of the selected dose of thrombolytic agent without ultrasound radiation of the thrombosis." *See* col. 3, lines 11 to 13. According to Siegel, the disclosed methods work because of the increased cavitation of vascular fluid surrounding the thrombosis. (*See* col. 5, line 66 to col. 6, line 3).

In contrast to the methods described by Siegel, independent Claims 116 and 164 define methods *for delivering a bioactive agent to a selected tissue*. Importantly, Applicant's claims recite that ultrasonic energy is applied *in an amount sufficient* to produce cavitation or rupture of the vesicles (Claim 116) or to activate the acoustically active composition (Claim 164). The embodiment of the invention defined by Claim 116 further utilizes ultrasound that is administered *in an amount sufficient* to increase the delivery of said bioactive agent *from* the vasculature *into* said selected tissue. Siegel completely fails to describe the application of ultrasound in an amount sufficient to achieve this result.

Although Siegel may be deemed to teach that the co-administration of ultrasound and a contrast agent, when combined with a thrombolytic agent, can enhance thrombolysis, Siegel provides no indication that the disclosed methods provide *delivery* of the thrombolytic agent to a selected tissue, or that ultrasound *enhances* such delivery. Thus, Siegel contains no teaching or suggestion that ultrasound may be used to augment delivery of a bioactive agent *from* the vasculature *into* a selected tissue. Since Siegel is silent regarding the goals of Applicant's methods, it goes without saying that Seigel completely fails to provide a description of the application of ultrasound *in an amount sufficient* to achieve such a result, as instantly claimed.

Moreover, Siegel explicitly *teaches away* from the application of ultrasound at the frequency recited in Claim 164 (as amended herein) and in added Claim 185. In this regard, Siegel states:

> Importantly, it has been found that when ultrasound is applied at a lower, rather than a higher frequency, the effectiveness of the method is markedly

> enhanced. More particularly, when ultrasound is applied at *less than about 100 kHz*, and even more particularly, between approximately 25 kHz and approximately 53 kHz, the dissolution of thrombi is most significant.

See Siegel, col. 5, lines 29 to 35 (emphasis added).

It is thus clear that Siegel fails to teach or suggest the following:

- application of ultrasound for the purposes claimed by Applicant;
- the application of ultrasound in an amount sufficient to achieve enhanced delivery of the bioactive agent from the vasculature into a selected tissue; and
- the application of ultrasound energy having a frequency of from 100 kHz to 1MHz.

Indeed, with regard to this latter element, as discussed above, Siegel *teaches away* from the defined ultrasound frequencies. In particular, as noted above, Siegel teaches the use of ultrasound frequencies of less than about 100 kHz, preferably from 25 kHz to about 53 kHz. Accordingly, Applicant respectfully submits that Siegel completely fails to anticipate the claimed invention.

Siegel also fails to suggest the beneficial results that may be derived from Applicant's methods. For example, as described in the specification, the methods of the present invention which target specific tissues for enhanced uptake of a bioactive agent potentially serve to lower the required dosage amounts, thereby minimizing toxic side effects and reducing costs to the patient. Similarly, increasing the deposition of a bioactive agent within a selected tissue may be used to deliver the agent to areas that suffer from poor capillary perfusion, providing delivery of

the agent to tissues that might otherwise be inaccessible. *See e.g.*, page 4, line 19 to page 5 line 7. The Siegel patent contains absolutely no teaching or suggestion of such benefits, as Siegel is directed to other ends.

Applicant respectfully submits that since Siegel neither teaches nor suggests the elements of Applicant's claimed methods, in fact teaches away from such methods, and also completely fails to teach or suggest the beneficial results that may be achieved by practicing Applicant's methods, Siegel does not render Applicant's invention obvious.

For the foregoing reasons, Applicant respectfully requests that the rejections under Section 102 and 103 over Siegel be withdrawn.

Rejections over Porter, in view of Siegel

Claims 116 to 131, 138 to 141, 146 to 151, 160, 164 to 166, 168 to 174 and 178 to 184 also stand rejected under 35 U.S.C. § 103 over Porter, U.S. Patent No. 5,648,098 ("Porter") in view of Siegel.

Like Siegel, Porter is directed to thrombolytic therapy. *See* abstract. It is apparently the Examiner's position that Porter is directed to the same drug delivery methods as Applicant's claims, because Porter teaches and claims delivery of a composition that includes a medicament (*see, e.g.* claim 22 of Porter). Applicant respectfully notes, however, that Porter's claimed method is still one of "treating thrombosis," not one for delivery of a bioactive agent, as instantly claimed, and like Siegel, contains no teaching or suggestion that the methods described therein may be used to enhance the delivery of the bioactive agent to a selected tissue.

Since Porter is directed to different ends than Applicant's claimed invention, Porter, like Siegel, also completely fails to teach or suggest the application of ultrasound *in an amount sufficient* to increase the delivery of said bioactive agent *from* the vasculature *into* the selected tissue. Accordingly, Porter fails to overcome the deficiencies of Siegel, with regard to this element of Applicants' claims.

Moreover, although Porter may teach the application of ultrasound having higher frequencies, Applicant respectfully submits that it would be improper to combine this teaching with that of Siegel, because Siegel explicitly *teaches away* from making such a combination.[1] In making a rejection based on obviousness, a reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F2d 1540 (Fed. Cir. 1983). Thus, a rejection combining Porter with Siegel requires that one select and combine elements of the two references using hindsight reasoning, with a rationale that comes from the application itself, not from any motivation taught by the prior art. As the CAFC has repeatedly held, such rejections are improper. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner

[1] Indeed, the data supplied by Siegel indicates that poor results were achieved when higher frequencies of ultrasound were used. *See, e.g.*, Siegel, col. 7, Example III, and compare % reduction shown in Table 14, at 105.4 kHz, with that in Table 10, at 24.8 kHz.

claimed"). Absent the teachings of the instant application, one of ordinary skill in the art would have had no reason to make such a combination.

Applicant respectfully submits, therefore, that Porter and Siegel, in any proper combination, fail to teach or suggest the invention defined by Applicant's claims. Accordingly, Applicants respectfully requests that the rejection under Section 103 be withdrawn.

Double Patenting Rejections

Claims 116 to 131, 138 to 141, 146 to 151, 160, 164 to 166, 168 to 174 and 178 to 184 stand rejected under the judicially created doctrine of obviousness-type double patenting over U.S. Patent Nos. 6,143,276 and 5,580,575. Applicant respectfully requests that these rejections be reconsidered in light of the claim amendments submitted herein. Should any of these rejections be maintained, Applicant proposes to file a terminal disclaimer as provided in 37 C.F.R. § 1.130(b) once the Examiner has issued a favorable ruling indicating that the amended claims will be allowed. Applicant will be filing the terminal disclaimer to facilitate prosecution and Applicant expresses no opinion as to whether the obviousness-type double patenting rejection is warranted in view of the aforementioned patents.

Claims 116 to 131, 138 to 141, 146 to 151, 160, 164 to 166, 168 to 174 and 178 to 184 also stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over the pending claims of copending Application Serial No. 09/218,660 ("the '660 application"). Applicants respectfully request that this rejection also be reconsidered in light of the claim amendments submitted herein. Should the rejection over the '660 application be

maintained, Applicant reserves the right to address such rejection once a claim is allowed in that application.

Cancellation of Non-Elected Species

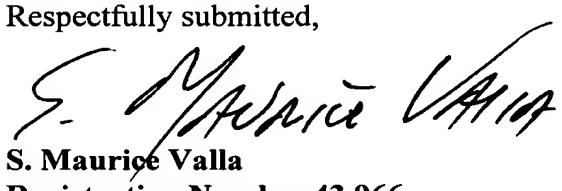
Claims 132 to 137, 142 to 145, 152 to 159, 161 to 163 and 175 to 177 have been withdrawn from consideration as directed to non-elected species. It is Applicants' understanding that, if the elected subject matter is found to be allowable over the prior art, the search and examination will be expanded to cover other species, until it includes the full scope of the generic claims.

CONCLUSION

Applicant believes that the foregoing constitutes a complete and full response to the Office Action of record. Applicant earnestly requests reconsideration of the application and withdrawal of the pending rejections. Upon a determination that the generic claims are allowable, Applicant respectfully requests that the withdrawn claims be examined.

Attached hereto is a marked-up version of the changes made to the application by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,



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Version With Markings To Show Changes Made

Claims 116 and 164 have been amended, as follows:

116. (Twice amended) A method for enhancing the delivery of a bioactive agent from the vasculature to a selected tissue in a patient, said method comprising:

(i) administering said bioactive agent to said patient[, by a route of administration sufficient to achieve a predetermined concentration of said bioactive agent within the vasculature of said selected tissue];

(ii) administering a vesicle composition to said patient, by continuous intravascular infusion [for a time sufficient to achieve a predetermined concentration of said vesicle composition within the vasculature of said selected tissue], wherein said vesicle comprises, in an aqueous carrier, vesicles comprising lipids, proteins or polymers and a gas or gaseous precursor; and

(iii) applying ultrasonic energy to [said selected tissue] the patient in an amount sufficient to produce cavitation or rupture of said vesicles, and sufficient to increase the [wherein said cavitation or rupture of said vesicles induces an increased] delivery of said bioactive agent from [said] the vasculature [to] into said selected tissue.

164. (Twice amended) A method for enhancing the delivery of a bioactive agent to a selected tissue in a patient, said method comprising:

(i) administering said bioactive agent to said patient[, by a route of administration sufficient to achieve a predetermined concentration of said bioactive agent within the vasculature of said selected tissue];

(ii) administering an acoustically active composition to said patient, by continuous intravascular infusion [for a time sufficient to achieve a predetermined concentration of said acoustically active composition within the vasculature of said selected tissue]; and

(iii) applying ultrasonic energy to [said selected tissue] the patient in an amount sufficient to activate said acoustically active composition, and sufficient to increase the [wherein the activation induces an increased] delivery of said bioactive agent [from said vasculature] to said selected tissue, wherein said ultrasound has a frequency of from about 100 kHz to about 1 MHz.

Claims 185 has been added.